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Population Pharmacokinetics/Pharmacodynamics of Anesthetics

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ABSTRACT

In this article we review how population pharmacokinetic/pharmacodynamic (PD) modeling has evolved in the specialty of anesthesiology, how anesthesiology benefited from the mixed-effects approach, and which features of modeling need careful attention. Key articles from the anesthesiology literature are selected to discuss the modeling of typical anesthesiological PD end points, such as level of consciousness and analgesia, interactions between hypnotics and analgesics, estimation with poor and sometimes rich data sets from populations of various sizes, covariate detection, covariances between random effects, and Bayesian forecasting.

KEYWORDS: PK/PD modeling, anesthetics, NONMEM

INTRODUCTION

Anesthesiologists have a variety of drugs at their disposal to perioperatively ascertain that all of a patient's physiologic functions remain compatible with life, while allowing surgical treatment without the patient's awareness. The scope of this review is the modeling of the action of drugs that produce 2 main goals of anesthesia: analgesia and loss of consciousness. The basic principles of pharmacokinetic (PK)/pharmacodynamic (PD) mixed-effects modeling (MEM) will not be discussed, because that has been done extensively elsewhere.[1-3] Earlier reviews exist. The one by Whiting et al[4] dealt only with PKs and not with the anesthetics that are within the scope of this article, and the more recent one by Wright[3] focused also only on PKs. The article by Minto and Schnider[2] mainly focused on methodology and on how to better evaluate and present the clinical significance of the constructed PK/PD models. All of the population analyses in the herein discussed articles were performed with NONMEM: the nonlinear MEM software package developed by the NONMEM Project Group.[1] Our selection of articles that apply NONMEM to the description of the effects of anesthetics is not exhaustive but does cover a fair part.

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Population PKs

The first population PKs article in a journal on anesthesiology appeared almost 20 years ago[5] and was accompanied by an editorial.[6] The PKs of the opioid alfentanil were studied in 45 patients, and the covariates (patient factors that affect model parameters) age, weight, and sex were identified; however, a relatively large intersubject variability remained.

The second population PK article[7] in a journal on anesthesiology described the PKs of propofol in children (propofol is a hypnotic often used for induction and maintenance of anesthesia). It was also accompanied by an editorial,[8] which discussed the features of population modeling. One important advantage of using population analysis is that it can handle few samples per subject (albeit in a larger population), which is advantageous in children when there are ethical limitations on the amount of blood that can be drawn. In the article, the "standard 2-stage," "naïvely pooled data" (NPD), and mixed-effects modeling approaches were compared, and it was concluded that the 3 approaches did not essentially differ with respect to the population parameter estimates and their description of the data as quantified by the median of the absolute weighted residuals. The accompanying editorial additionally discussed the optimal application and the relative merits of these approaches.

In the multicenter trial of Schüttler et al,[9] the PKs of propofol in 270 patients were studied, and age, weight, and mode of administration were identified as important covariates.[10] The latter covariate could be caused by model misspecification, although the sampling schedules in bolus and infusion studies provided different information content. Furthermore, some evidence was found of nonlinear PKs. So, differences among the results from various investigations may not only be caused by differences among the populations studied but also by differences among the infusion regimens applied. Model misspecification occurs when the ordinarily applied linear compartmental models do not adequately approximate the underlying physiology.

Early Phase Pharmacokinetics: Recirculatory Models

For induction of anesthesia and compensation of inadequate anesthesia, fast-acting drugs (which have fast blood-to-brain concentration equilibration) have been developed, which are administered intravenously. This has 2 consequences. First, standard compartmental PK models are unable to accurately describe drug concentrations shortly after bolus administration[11] because mixing in the "central compartment" is not instantaneous because of the circulatory system and, second, because of pulmonary uptake.[12] During the first minutes of drug administration, compartmental models, therefore, provide inadequate input for PD models. Recirculatory models have been developed by Krejcie et al[13] in which the pulmonary and peripheral intravascular and extravascular subsystems, each consisting of volumes and time delays, are connected according to circulatory physiology. In contrast with physiologically based PK models, all of the parameters are, in principle, estimable, by administering not only the drug under study but also an intravascular marker. A recirculatory model applied to the PDs of the muscle relaxant rocuronium provided an adequate description of the concentration-effect relationship, which was not possible using compartmental models.[14] However, at the time, a population recirculatory PK/PD analysis was not feasible, and studies based on such analyses have yet to appear.

Population PK/PD

PD models of anesthetics typically consist of a hypothetical effect compartment with an equilibration rate parameter (to account for a delay between drug concentration in arterial blood and drug effect) and a sigmoid E_{max} model with potency and shape parameters.[15]

The first population PK/PD article in a journal on anesthesiology appeared in 1990 and described the PKs and PDs of the hypnotic thiopental in 64 subjects.[16] The spectral edge frequency (SEF) of the electroencephalogram (EEG) was used as the PD end point. The SEF is determined from the power spectrum and is defined as the frequency under which 95% of the power of the signal is contained. Anesthetics generally have a concentration-dependent influence on the SEF. Age was shown to affect the PKs rather than the PDs; problems with compartmental modeling, as described in the previous section, may have influenced the results.[11]

Somma et al[17] described the PDs of the sedative midazolam; the probabilities of observing sedation scores $\geq$7 predefined levels were assumed to be sigmoidally linked to effect-site concentration with different potency parameters for each level. A "leave-one-out" procedure was used to cross-validate (by predicting each individual's response based on parameters obtained from data without that individual) the predictive power of the constructed models. It was found that the sedation score could be predicted within 1 level at 88% accuracy using the NPD approach and at 83% accuracy using the mixed-effects approach. The decrease in accuracy was probably attributable to biased estimates of the population estimates using the latter approach. Propofol sedation was modeled,[18-20] and the latter study showed that the PDs were independent of the rate of administration.

Minto et al[21] modeled the effect of the opioid remifentanil on the spectral edge of the EEG and detected age and lean body mass, but not sex, as important covariates. Anderson et al[22] constructed a model of the PDs of the antipyretic analgesic acetaminophen in children using a visual analog scale and applied it to the development of dosing guidelines.

Rehberg et al[23] compared the changes in the Hoffman reflex amplitude with those in SEF and bispectral index (a measure of depth of anesthesia[24] that reflects the hypnotic state of the patient more accurately than SEF, developed by Aspect Medical Systems, Newton, MA) caused by sevoflurane (an inhalational anesthetic) administration in patients. The differences in model parameters indicated differences in underlying mechanisms.[23] It was also found that surgical stimulation shifts the desflurane (a similar inhalational anesthetic) concentration-EEG effect relationship.[25]

In patients, the level of analgesia and quantitative nature of noxious stimuli during or after surgery is difficult to assess, and, therefore, studies have been done under more controlled circumstances. By using an experimental pain model in 20 young, healthy volunteers, sex differences in morphine analgesia were detected by Sarton et al.[26] The data obtained consisted of electrical currents in steps of 10 mA with a cut-off of 80 mA; because of the categorical data, sometimes above the cut-off, the information content of each individual's data was relatively low. A population analysis yielded precise estimates of the PD parameters and their interindividual variability. Including the covariate, sex was highly significant, but, still, 55% interindividual variability of the blood-to-effect site concentration equilibration rate constant remained. High variability of the equilibration rate constant and potency has also been found for the opioid alfentanil,[27,28] but no sex differences were detected. Genetic differences other than sex may partly explain variability in the analgesic effect of morphine-6-glucuronide.[29]

Respiratory depression is a side effect of opioid administration and may be life threatening, especially in the postoperative period. Population analysis of depression of ventilation and of the ventilatory response to hypoxia because of morphine, morphine-6-glucuronide, and remifentanil

also revealed a relatively large interindividual variability, whereas no explanatory covariates were found,[30-32] but the studied populations were small and/or homogeneous.

Pharmacodynamic Interactions

The interaction between the remifentanil and sevoflurane concentration on surrogate effect measures, such as SEF and bispectral index, was studied,[33] and the data indicated that the opioid accelerates the equilibration between the blood and the effect site concentration of sevoflurane.

Minto et al[34] developed a response surface model for drug interactions, which is based on 2 fundamental ideas. First, the combination of 2 (or more) drugs is considered to act like a single drug with a certain concentration-effect relationship. Second, the properties of this virtual drug and, therefore, the parameters of its concentration-effect relationship, are only dependent on the ratio of the concentrations of the 2 drugs. These ideas allow a response surface to be described by a few parameters that may be estimable from studies of a reasonable size. Application of this model was illustrated using the level of hypnosis because of the administration of combinations of midazolam, propofol, and alfentanil. This approach allowed the detection of synergism between anesthetics with respect to a variety of anesthetic end points[35] and respiratory depression.[36,37] Synergism (stronger interaction than would be expected from the combination of concentrations with respect to the drug potencies were they given separately) is most useful when it is stronger with respect to the desired effects than to the side effects.

Covariate Detection and Model Selection

Detecting and modeling the influence of covariates is an art in itself,[38-41] and it was so especially in the early days when performing many FOCE (NONMEM first-order conditional estimation method) runs was unfeasible because of their computational costs. For small data sets, there is a risk of erroneous detection of covariates, especially in the case of correlated covariates.[42,43] NONMEM typically runs slowly also with the FOCEI (FOCE that takes interaction between first-level and second-level random effects into account) option. However, this estimation procedure is essential for trustworthy covariate detection, when dealing with highly nonlinear models, and when "rich" data (high information content per subject) is available.[44,45] Pharmacodynamic models are often highly nonlinear, but a mixed-effects approach helps their characterization,[46] and a mixed-effects approach remains useful also with rich data.[47]

A model that is constructed based on *P* values may not be the best description of the data.[2,48,49] Model selection based on Akaike's[50] information-theoretic criterion (possibly modified for small data sets) may be preferable, even if it yields model components that do not seem to be clinically relevant. In the first stage, the aim is to capture the information in the data. Using (conservative) *P* values for model selection could yield a model biased down to the assumptions that underlie the null hypotheses, and those assumptions could be (and typically are) false. As an example, see Ref. 51, where the influence of cardiac output on lidocaine was modeled in 31 patients. The effect on a PK parameter was considered significant when *P* value is <0.05, which corresponds with a decrease of the objective function of 3.84 per parameter, which is not too far from 2, which one would use for AIC. It was shown that the median absolute prediction errors decreased within that patient population (see Figure 2 in that article), if covariates were taken into account. How that could benefit the prediction of the PKs in an unstudied patient was not assessed (no cross-validation was performed). But using conservative *P* values rather than AIC could result in a model that is biased to one that assumes that taking cardiac output into account does not benefit the unstudied patient, even though that should be determined at a later stage.

The Full Covariance Matrix

The goal of MEM is to simultaneously obtain an estimate of the covariance matrix of the first-level random effects[3] (which is called Ω in NONMEM jargon) and less biased and more precise estimates of the structural parameters. Ω allows the anesthesiologist to supply a prediction of drug concentration and/or effect with a measure of the associated uncertainty because of interindividual differences.[2,3,52] Furthermore, it allows for improved trial design[53,54] and Bayesian forecasting (see next section). Extra modeling effort is necessary; although NONMEM avoids dependence on assumptions on the nature of the random effects as much as possible, deviations from those assumptions may render the population estimates inferior to those obtained from an NPD analysis in particular with rich data sets (SL Shafer, written communication, February, 2005), and bias of the estimated parameters may be especially large with categorical data.[55,56] Furthermore, rich, in particular, PD, data sets may be difficult to model (eg, many sources other than effect-site drug concentration affect EEG surrogate effect parameters), which may lead to correlated residuals and SEs of estimate parameters that may be biased downward.[47]

In none of the reviewed PK-PD articles were covariances between first-level random effects reported, whereas their description may be beneficial for the application of population models. The adequacy of the stochastic part of the model may be evaluated using the posterior predictive

Table 1. Alfentanil Compartmental PK Parameter Estimates*

Parameter	Estimate	SE	VAR(η)	SE
V1 (L)	4.32	0.663	–	–
V2 (L)	4.91	0.726	0.0829	0.0472
V3 (L)	12.2	0.836	0.0770	0.0216
CL1 (L/min)	0.274	0.0182	0.104	0.0322
CL2 (L/min)	1.33	0.342	0.292	0.192
CL3 (L/min)	0.307	0.0262	–	–

*η indicates first-level random effect.

check, which, in its simplest form, entails comparing the distributions of simulated data from the population model (eg, 95% prediction intervals) with the measured data.[57]

Estimation of the full covariance matrix is often not possible when the number of subjects is relatively low (eg, because of ethical reasons). Therefore, often only the elements of the diagonal (the variances of the interindividual error term on each parameter) are considered. Still, not all of them can be estimated, and these are typically biased down to zero (usually indicated by a hyphen in the tables in the literature); in other words, the fit is best when they are fixed to zero, although they are unlikely to be truly zero.

A PK model of alfentanil, determined from 24 healthy volunteers, parameterized using volumes and clearances (which may be preferable, because they could be more directly linked to covariates such as weight than rate constants), yielded the parameter estimates given in Table 1 (for additional details, see Ref. [28]). Note that the random effect variances associated with V1 and CL3 were estimated to be zero. The AIC (−2LL + 2P) of this model was 2,991. No significant effect of weight was found on the PK parameters.

The following approach could be used to find a better approximation of the full-covariance matrix. Consider that there are sources for interindividual variability, such as weight or sex. There could be, for example, just 1 important source of variability, whereas there are 6 parameters necessary to describe the PKs of a drug. So assume that 1 random effect has an influence on those 6 PK parameters via 6 strength factors λ. These strength factors are better estimable than the variances of the same number of random effects. This can be repeated for additional random effects, and a (not necessarily square) matrix Λ of strength factors that is significantly different from zero can be obtained. Now note that the Ω matrix is the product of Λ and its transpose (the vector $\theta_i = \theta_p \exp(\eta)$; θ_i is individualized from the population values θ_p because of η; $\eta = \Lambda \eta'$; the variances of the ηs fixed to 1). The population parameters and covariance matrix Ω obtained in this way for the alfentanil PKs are presented in Table 2, and the strength matrix in Λ is presented in Table 3. Notice that the diagonal of Ω now also contains those elements that were previously biased down to zero. The AIC of this model was 2,957.

The next step is to identify which covariates are correlated with the individual Bayesian estimates of the ηs, which may be more successful than with the standard ηs, because a functional correlation between the structural parameters has already been captured in Ω. In this case, we do find an effect of weight, on 3 ηs via 1 additional parameter and an improved model with an AIC of 2,944 (corresponding results not shown). However, possible merits of this approach need to be additionally investigated.

Often, a correlation is found (with a magnitude possibly dependent on the study design) between not only the estimates of the equilibration rate and potency parameters themselves but also between their associated ηs, such that the maximum achieved effect across the population remains relatively the same, a phenomenon for which no explanation exists at present. Taking into account such correlations in the covariance matrix, however, could increase the accuracy of prediction intervals considerably.

Finally, when the information in the data has been optimally captured in estimates of the structural and variability parameters, it is possible to combine such information from a collection of studies (rather than analyzing the whole set of data) using Bayesian methods.

Bayesian Forecasting

Some anesthesiology articles on population modeling[3,7,16,58-60] discussed the possibilities of Bayesian forecasting based on the article by Sheiner et al.[61] When a

Table 2. Alfentanil Compartmental PK Parameter Estimates With Full (Lower Part of Symmetrical) Covariance Matrix Ω

Parameter	Estimate	SE	Covariance Matrix $\Omega = COV(\eta_i,\eta_j)$					
V1 (L)	5.14	0.653	0.0650					
V2 (L)	5.96	0.864	0.126	0.263				
V3 (L)	10.9	0.605	–	–	0.0420			
CL1 (L/min)	0.274	0.0179	0.0660	0.128	−0.0279	0.102		
CL2 (L/min)	1.03	0.247	−0.117	−0.227	–	−0.206	0.679	
CL3 (L/min)	0.214	0.0308	−0.155	−0.302	–	−0.157	0.278	0.370

Table 3. Strength Matrix Λ*

Parameter	$\lambda(\eta_1)$	$\lambda(\eta_2)$	$\lambda(\eta_3)$	$\lambda(\eta_4)$
V1	−0.255	–	–	–
V2	−0.496	–	–	0.131
V3	–	−0.205	–	–
CL1	−0.259	0.136	−0.127	–
CL2	0.458	–	0.685	–
CL3	0.608	–	–	–

*SEs not given; (non)zero elements selected based on AIC.

population model is available, the PK/PD model of an unstudied patient can be updated from measurements as they become available using Bayesian methods. Two articles evaluate the possible usefulness of such procedures, 1 on predicting individual alfentanil PKs and 1 on predicting bupivacaine (a drug for spinal or epidural) analgesia. First,[58] it was found that knowing only 1 drug concentration (taken at an appropriate instant) of the patient under study substantially improved the prediction of that individual's PKs. One measurement may provide more information than all of the relevant covariates available[61] (but exploring covariates of course provides information on the underlying mechanisms). Second,[60] it was found that the coefficient of correlation between the Bayesian predictions and the measurements of the level of bupivacaine analgesia improved from 0.5 (no knowledge) to 0.7 (30 to 60 minutes of information) to 0.9 (all data). Models that can be "individualized" on-line are useful for target-controlled infusion devices (when the blood concentrations of the administered can be measured on-line) or for more complicated control systems,[2,20,62] possibly without knowing blood concentrations.[63]

CONCLUSION

During the last twenty years, MEM has been applied to the PKs and PDs of a variety of anesthetics, including their interactions; important covariates have been detected, and residual interindividual variability has been quantified. The knowledge obtained can be, and is being, incorporated in concentration or effect target-controlled infusion devices that assist the anesthesiologist in optimizing the balance between desired effects and side effects. To obtain a high reliability of such devices, the underlying model parameters have to be as accurate as possible. Furthermore, because interindividual variability is large even when covariates are taken into account, the mechanisms responsible need to be elucidated so that novel drugs can be developed with a high predictability. Finally, the likelihood of adequate anesthesia can be maximized by Bayesian incorporation of information acquired on-line in the operating room.

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